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Protective role of selenium against the toxicity of multi-drug chemotherapy in patients with ovarian cancer

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The present clinical trial has been undertaken to examine the influence of Selenium (Se) on the toxicity of cisplatin and cyclophosphamide administered as part of a chemotherapy regimen in patients with ovarian cancer.
The concentration of selenium in serum after 4, 8 and 12 weeks of supplementation with a daily dose of 200 μg Se was significantly higher ($p < 0.05$) than in the control group without supplementation. Similarly, the concentration of Se in hair was markedly increased ($p < 0.05$).

Table 1: Hematology and biochemistry results in patients with ovarian cancer with and without Se supplementation during chemotherapy (mean ± SD)

Parameter	Time	Group		p
		Study (with Se) n = 31	Control (without Se) n = 31	
WBC ($\times 10^9$/L)	I	6.96 ± 1.75	7.42 ± 2.24	NS
	II	5.74 ± 1.63	6.51 ± 2.13	NS
	III	5.98 ± 1.65	5.38 ± 1.88	NS
Neut ($\times 10^9$/L)	I	5.03 ± 1.48	5.17 ± 1.91	NS
	II	3.82 ± 1.14	3.90 ± 1.66	NS
	III	3.39 ± 1.09*	2.52 ± 1.13	*
Neut (%)	I	66.58 ± 8.06*	59.40 ± 14.54	*
	II	71.65 ± 9.44	69.28 ± 12.10	NS
	III	56.93 ± 11.91*	48.11 ± 14.76	*
RBC ($\times 10^{12}$/L)	I	4.03 ± 0.44	4.06 ± 0.55	NS
	II	4.02 ± 0.38	4.03 ± 0.45	NS
	III	3.87 ± 0.47	3.80 ± 0.50	NS
Hb (g/dl)	I	7.10 ± 2.06	7.60 ± 0.85	NS
	II	7.29 ± 1.64	7.70 ± 0.78	NS
	III	7.64 ± 0.93	7.31 ± 0.84	NS
PLT ($\times 10^9$/L)	I	265.93 ± 93.31	257.64 ± 102.74	NS
	II	230.87 ± 64.35	236.96 ± 71.24	NS
	III	208.08 ± 52.29	201.58 ± 64.70	NS
Urea (mg/dl)	I	29.78 ± 7.60	33.21 ± 11.19	NS
	II	32.21 ± 8.08	31.00 ± 12.05	NS
	III	33.88 ± 14.87	34.42 ± 16.44	NS
Creat (mg/dl)	I	0.85 ± 0.18	0.75 ± 0.24	NS
	II	0.82 ± 0.15	0.87 ± 0.19	NS
	III	0.90 ± 0.17	0.87 ± 0.20	NS
Bil (mg/dl)	I	0.48 ± 0.20	0.56 ± 0.35	NS
	II	0.50 ± 0.34	0.52 ± 0.21	NS
	III	0.66 ± 0.39	0.68 ± 0.30	NS
AST (U/L)	I	33.00 ± 19.64	36.55 ± 24.92	NS
	II	32.35 ± 27.05	32.48 ± 22.95	NS
	III	42.30 ± 33.77	44.83 ± 35.52	NS
ALT (U/L)	I	25.41 ± 17.26	39.31 ± 39.34	NS
	II	29.00 ± 29.98	36.75 ± 37.98	NS
	III	42.96 ± 48.31	44.27 ± 43.60	NS
CA-125 (U/ml)	I	505.5 ± 1180.1	377.3 ± 902.8	NS
	II	142.2 ± 293.8	149.5 ± 255.8	NS
	III	93.5 ± 199.6	227.7 ± 712.9	NS

* $p < 0.05$ vs. control group: 0 – before supplementation, I: after one month, II: after two months, III: after three months of supplementation (month = 28 days)

Table 2: Modified, semi-quantitative evaluation of toxicity symptoms in patients with ovarian cancer undergoing chemotherapy with and without Se supplementation (mean ± SD)

Parameter	Time	Group		p
		Study (with Se) n = 31	Control (without Se) n = 31	
Nausea	I	2.19 ± 1.07	1.81 ± 1.04	NS
	II	1.19 ± 0.90*	1.93 ± 0.91	*
	III	0.97 ± 0.70*	2.03 ± 0.84	*
Vomiting	I	1.74 ± 1.43	1.68 ± 1.32	NS
	II	1.07 ± 0.86*	1.87 ± 1.33	*
	III	0.97 ± 0.87*	2.16 ± 1.24	*
Diarrhea	I	0.22 ± 0.56	0.13 ± 0.43	NS
	II	0.13 ± 0.43	0.22 ± 0.56	NS
	III	0.13 ± 0.56	0.22 ± 0.56	NS
Stomatitis	I	0.35 ± 0.91	0.45 ± 1.05	NS
	II	0.10 ± 0.30	0.45 ± 0.96	NS
	III	0.32 ± 0.18*	0.58 ± 1.02	*
Hair loss	I	1.83 ± 1.32	1.55 ± 1.21	NS
	II	1.87 ± 0.89	2.22 ± 0.85	NS
	III	2.12 ± 0.96*	2.55 ± 0.50	*
Flatulence	I	2.10 ± 1.16	1.58 ± 1.28	NS
	II	1.16 ± 1.03	1.71 ± 1.27	NS
	III	0.61 ± 0.71*	1.97 ± 1.11	*
Abdominal pain	I	0.93 ± 1.09	1.32 ± 1.66	NS
	II	0.39 ± 0.61*	1.22 ± 1.09	*
	III	0.45 ± 0.62*	1.45 ± 1.18	*
Weakness	I	2.13 ± 1.17	2.19 ± 0.96	NS
	II	1.26 ± 0.85*	2.26 ± 0.79	*
	III	0.97 ± 0.79*	2.35 ± 0.99	*
Malaise	I	1.93 ± 1.23	2.19 ± 0.91	NS
	II	0.84 ± 1.00*	2.45 ± 0.67	*
	III	0.87 ± 0.80*	2.54 ± 0.67	*
Anorexia	I	2.39 ± 0.88	2.13 ± 0.96	NS
	II	1.00 ± 0.86*	2.35 ± 0.79	*
	III	0.84 ± 0.73*	2.26 ± 0.99	*

Severity scale: 0: no symptoms 1: mild
2: moderate 3: severe
4: life-threatening
* $p < 0.05$ vs. control group: 0: before supplementation, I: after one month, II: after two months, III: after three months of supplementation (month = 28 days)
Age: study group – 49.4 ± 12.9 years, control group – 52.7 ± 12.6 years ($p > 0.05$)

Table 1 shows hematology and biochemistry results in patients with ovarian cancer with and without Se supplementation during chemotherapy.
Table 2 shows a semi-quantitative analysis of side effects in patients with ovarian cancer receiving Se, in comparison with the control group.
The present clinical trial has demonstrated that supplementation with Se in patients with ovarian cancer undergoing chemotherapy leads to an increase in the level of selenium in blood and hair. This result is in agreement with the study of Das and Ma [1], Dróżdż et al. [2] and others [3, 4] who have found reduced levels of Se in the serum of patients with ovarian cancer and a beneficial influence of Se supplementation on the level of this microelement in serum and tissues. A steady loss of Se during chemotherapy has been revealed in the present control group. Supplementation with Se leads to an increase in the activity of GSH-P_x in erythrocytes, confirming the results of Sundström et al. [5] with a combination of Se and vitamin E.
It may be concluded from these results that Se supplementation at a dose of 200 μg daily during 12 weeks significantly reduced the neutrophil count and percentage. The remaining parameters studied were unaffected.

In general, the present results agree with those of Kośmider et al. [6] who have found that Se alleviates nausea, vomiting, diarrhea, abdominal pain and weight loss. However, no influence on hair loss was noted. This symptom seems to be the most persistent during chemotherapy.
Se deficiency, observed in patients with ovarian cancer, increases the toxicity of cytostatics. Recently, Matsuda et al. [7] have suggested that an imbalance in the oxidative system is mainly due to Se deficiency and that Se plays a protective role in functional disturbances of the heart caused by free radical production induced by cytostatics used for chemotherapy.
In conclusion, a sufficiently long supplementation with Se in patients with ovarian cancer subjected to multi-drug chemotherapy results in a number of beneficial biochemical changes and reduction in side effects of chemotherapy.

Experimental

The study group included 31 patients with ovarian cancer, taking Se-Protecton® Zellaktiv (Smith Kline Beecham, Fink Naturarznei GmbH, Germany), 2 capsules 4 times daily. The control group included 31 patients with ovarian cancer who did not receive Se supplementation. The mean age of patients in the study and control groups was 49.4 ± 12.9 and 52.7 ± 12.6 years, respectively. The diagnosis of ovarian cancer was made by laparotomy and histological examination of tumor samples. Clinical staging was according to FIGO criteria. The study group included 15 patients with clinical stage I/II and 16 with stage III/IV. For the control group, these figures were 16 and 15 patients, respectively.
All patients were treated according to the accepted clinical protocol in ovarian cancer: surgery followed by intravenous multi-drug chemotherapy sessions in 21-day intervals. Chemotherapy comprised cisplatin 100 mg/m^2 (Platamine, Farmitalia, Carlo Erba, Italy) and cyclophosphamide 600 mg/m^2 (Endoxan, Asta Medica, Germany). At the start of this trial 23 patients of the study group were during their first and 8 during subsequent sessions. In the control group, 21 patients were during their first and 10 during subsequent sessions. The chemical composition and biological properties of Protecton® Zellaktiv (Smith Kline Beecham, Fink Naturarznei GmbH, Germany) were as follows (per 2 capsules): β-carotene – 15 mg, vitamin C – 200 mg, vitamin E – 36 mg, riboflavin (vit. B_2) – 4.5 mg, niacin (vit. B_3) – 45 mg, selenium yeast – 50 mg (Se = 50 μg). The preparation was administered to patients of the study group during 3 months.
Clinical status was checked every month, using a standard gynecological examination and ultrasound of the abdomen and small pelvis. This was complemented by biochemical tests. The concentration of Se in serum and hair, activity of GSH-P_x, concentration of MDA in serum and platelets were measured before Se supplementation and 4, 8 and 12 weeks thereafter. All biochemical tests were done immediately before the chemotherapy session. In the control group, Se was replaced by placebo. Biochemical tests were done at the same time as in the study group.
The following tests were done before each chemotherapy session: hematology, platelet count, urea, creatinine, bilirubin, aminotransferase activities and CA-125. An evaluation of side effects was performed after each chemotherapy session.

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How relevant is the application of antioxidants in order to avoid UVB-induced photodamages?

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Reactive oxygen species (ROS) are thought to play an important role in mediating UVB-induced harmful skin alterations [1]. For this reason, it is often suggested that a protection from UVB-induced skin damages is possible by the topical use of radical scavengers. However, the idea of cause and effect seems to require a verification in special questions. For example, an erythema induced by UVB irradiation is reduced by topical treatment with antioxidants [2–4]. The frequently used vitamin E has two relevant properties, which are often hardly taken into account: vitamin E absorbs UV light with a maximum at 295 nm and possesses an anti-inflammatory effect via the inhibition of phospholipase [5, 6]. This example is to demonstrate that a causal link between radical scavenger properties and erythema protection cannot be proven by such a study design. Moreover, since ROS play a role in signal transduction too, the clinical benefit of a massive intervention in the oxidative balance remains questionable. It seems conceivable that ROS quenching by overloading the cells with antioxidants leads to an inhibition of physiological processes as well. In this context, the radical nitric oxide should be mentioned [7].
To support our calling into question of the relevance of using radical scavengers to avoid UVB-mediated skin damage we irradiated cultured keratinocytes with UVB light. Experiments were performed using the human keratinocyte cell line HaCaT which has been established as a model for studying mechanisms of UVB-induced cell alterations [8, 9]. Our aim was to investigate the influence of the UV light on the formation of cellular peroxides and cell viability. Moreover, the issue was addressed whether these parameters could be modulated by the pretreatment with the established antioxidants vitamin E or vitamin C and whether thereby an UVB-induced cell damage can be prevented.
In keratinocytes, UVB irradiation (30–240 mJ/cm^2) led to a dose depending raise in the amount of intracellular peroxides. In respect of viability, a drop to 60% of the untreated control was observed (Table). Vitamin C abolished the UVB-induced increase in the formation of peroxides (1000 μM) completely. Vitamin E reduced the UVB-in-

Table: Effect of UVB irradiation on the formation of peroxides and viability in keratinocytes

UVB dosage (mJ/cm^2)	Formation of peroxides (% of untreated control)	Surviving fraction (% of untreated control)
Untreated control	100.0 ± 7.94	100.0 ± 3.76
30	129.83 ± 9.42*	93.61 ± 3.84
60	157.35 ± 3.95*	86.75 ± 2.78*
90	222.37 ± 5.78*	81.80 ± 3.34*
120	234.60 ± 6.95*	74.84 ± 5.86*
150	271.28 ± 4.64*	65.65 ± 4.62*
180	350.31 ± 36.08*	64.20 ± 2.58*
210	395.08 ± 27.53*	63.80 ± 3.48*
240	460.81 ± 22.30*	60.17 ± 2.85*

* $P < 0.05$; UVB vs. untreated control, two-tailed t-test. All data shown are mean ± S.E.M. of n = 6 observations